REMARKS

With entry of the amendment, claims 25-27 are pending. Claims 21-24 have been cancelled. Claims 25-27 have been added. The amendments are fully supported by the application at least at paragraphs [0098], [0100], [0106], Example 2, and Example 3 of the specification as originally filed. The amendments introduce no new matter.

Rejections under 35 U.S.C. § 103(a)

Caskey, GenBank, Fregeau, Kimpton and Urquhart

The Examiner has maintained her rejection of claims 21 and 24 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,364,759 to Caskey et al. ("Caskey"), in view of GenBank STR loci (Accession Nos. M68651, M25858, D00269 and X14720) ("GenBank"), and further in view of Fregeau et al. (Bio Techniques, Vol. 15, No. 1, pp. 100-119 (1993)) ("Fregeau"), or Kimpton et al. (PCR Methods and Applications, Vol. 3, pp. 13-22 (1993)) ("Kimpton"), or Urquhart et al. (Int. J. Leg. Med., Vol. 107, pp. 13-210 (1994)) ("Urquhart").

To the extent that the rejections may be applied to claims 25-27, Applicants reiterate arguments made in the previous response, which is incorporated by reference.

Caskey is cited as teaching amplification and primers for amplifying certain loci (i.e., HUMFABP, HUMTH01, and HUMHPRTB). The Examiner acknowledged that Caskey fails to teach all the loci and the recited combinations of loci. None of Fregeau, Kimpton, or Urquhart teaches the remaining loci or any of the particular combinations of loci recited in claims 25-27. The Examiner relies on GenBank Accession numbers as teaching the STR loci HUMTPOX and HUMCSF1PO. However, GenBank does not disclose whether HUMTPOX and/or HUMCSF1PO is polymorphic, or whether these loci can be amplified reproducibly in a multiplex with the HUMVWFA31 and HUMTHO1. Furthermore, there is no cited reason to select the specifically claimed loci from among all of the STR loci in GenBank to make any of the combinations encompassed by claims 25-27.

Applicants respectfully submit the claimed invention is unobvious over the prior art in as much as it was inventive to identify polymorphic STR loci that could be combined in a multiplex amplification with the other recited loci. The Examiner quoted KSR as stating that "when there is a design need or market pressure to solve a problem and there are a finite number of identified,

predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." The Examiner apparently concluded that for the loci in at least some of the combinations within the Markush groups of claims 21 and 24, the art points to a finite number of loci.

Applicants respectfully submit that the Examiner cannot reasonably conclude that there are a *finite* number of *identified, predictable* solutions that would provide one of skill reason to pursue the combinations of claims 25-27. The number of STR loci that could possibly be used, while mathematically finite, is so large that a person of ordinary skill would not have good reason to pursue the particular combinations claimed. Caskey (col. 10, line 15) teaches that there are about 400 million STRs in the human genome. Fregeau (p. 101, col. 1) teaches that there are about 500,000 STRs in the human genome. Whether there exist hundreds of thousands of STR loci in the human genome as taught by Fregeau (p. 101, col. 1) or hundreds of millions of STR loci in the human genome as taught by Caskey (col. 10, line 15), the number of possible STR loci is so large that one of ordinary skill in the art would not have good reason to choose HUMCSF1PO from among all of the other loci that could have been used to detect different alleles in combination with the other loci recited in claims 25-27. Further, identification of polymorphic STR loci that can be co-amplified with sufficient reproducibility to allow alleles to be determined is not predictable.

The HUMCSF1PO locus of claim 25 was not disclosed by GenBank as being an STR locus that could be successfully used to distinguish alleles among individuals. Nor was the HUMTPOX locus of claim 26 disclosed by GenBank as being an STR locus that could be successfully used to distinguish alleles among individuals. The mere presence of a DNA sequence in GenBank does not suggest that the sequence is but one of a species of polymorphic alleles that could be used to discriminate between individuals, let alone one that could be coamplified with other loci to yield reproducible amplification results. Thus, one of ordinary skill in the art would have no reason to coamplify the claimed combinations of STR loci, and the claimed method is patentable over the prior art.

The Examiner asserts that there was a reasonable expectation of success in multiplex amplification of STR loci, and that this "reasonable expectation of success is based not on

Applicant's disclosure but on the vast teachings in the art...the specification, itself, suggests that the combinations, as provided in the instant claims, were a product of trial and error experimentation." Applicants respectfully submit that the art teaches the unpredictability and difficulty in selection of STR loci for successful and reproducible co-amplification. The Declaration by Cynthia Sprecher is a testament by a person having ordinary skill in the art about the difficulties and unpredictability and that discovery of the claimed STR combinations was not obvious.

The Examiner claims that "the prior art teaches an enabling methodology to perform multiplexing of STR loci, suggests to modify the references to encompass additional multiplex loci, and suggests alternative combinations would be successful." The number of possible STR loci is not reasonably finite. Disclosure of a few STR loci that are polymorphic and amplify reproducibly and distinguishably does not render obvious the selection of other particular loci and other specific combinations.

Applicants respectfully submit that the Examiner has failed to evaluate the invention as a whole and is ignoring the bulk of the prior art that speaks of the limitations, errors in GenBank (Urquhart, p. 16, col. 1), unpredictable parameters (Fregeau, p. 115, col. 2, p. 104, col. 2 and 3), indistinct amplification results and stutter artifacts (Kimpton, p. 17, col. 3), and the sheer vastness of possible STR combinations (Caskey, col. 10, line 15; Fregeau, p. 101, col. 1). For the sake of argument, even if all claimed STR loci and combinations were disclosed in the collective prior art, the "mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (*KRS Internationl Co. v. Telefax Inc.*, 127 S. Ct. 1727 (2007)). Applicants respectfully submit that claims 25-27 are patentable over Caskey, GenBank, Fregeau, Kimpton and/or Urquhart.

The Examiner, citing In re Brandstadter as standing for the proposition that although "a declaration which states only conclusions may have some probative value, such a declaration may have little weight in light of all the evidence of record in the application", dismissed as "opinion testimony" the declaration of Ms. Cynthia Sprecher, submitted with the previous response on December 13, 2007.

Ms. Sprecher, an inventor of the subject application, attested at paragraph 7 of her declaration, that at the time the invention was made, it was virtually impossible to predict in advance which loci could be amplified and evaluated together in a multiplex reaction. Ms. Sprecher further stated that in her experience, selecting STR loci for DNA typing, and subsequently amplifying the selected STR in a multiplex reaction, was very laborious and unpredictable (Sprecher declaration, paragraph 7). In light of her experience, Ms. Sprecher stated that one could not predict whether amplifying any particular set of loci in a multiplex would be successful (Sprecher declaration, paragraph 8).

The Examiner has adopted the view that the invention was arrived at through "trial and error" and erroneously concluded that the claimed methods are merely "routine experimentation". The Examiner, apparently likening the instant rejection to that described in In re O'Farrell, cited the case as holding "the claimed method would have been obvious over the prior art because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful."

With the knowledge that her statements are punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code, Ms. Sprecher has declared that "it was virtually impossible to predict in advance which loci could be amplified and evaluated together in a multiplex reaction" (Sprecher declaration, paragraph 7). In contrast to the facts in O'Farrell, the references do not suggest a method using the specifically recited loci in a multiplex, the references do not provide a methodology that would enable the invention as currently claimed, and there is no suggestion whatsoever that the modification would be successful. The Examiner nevertheless maintains the opinion that "given the teaching of the references, there is a reasonable expectation of success."

The Examiner cited In re Aller as holding that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine optimization." Applicants submit that the inclusion of particular loci together in a multiplex amplification reaction are not general conditions disclosed in the prior art. As noted above, Ms. Sprecher, based on her experience, has declared that "it was virtually impossible to predict in advance which loci could be amplified and evaluated together in a multiplex reaction"

(Sprecher declaration, paragraph 7). Applicants respectfully submit that trial and error does not equal routine optimization, and remind the Examiner that the law provides that "patentability shall not be negatived by the manner in which the invention was made." (35 USC 103(a)).

Schumm, Fregeau, Kimpton and Urquhart

Claims 21 and 24 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,783,406 issued to Schumm et al. ("Schumm"), in view of Fregeau, Kimpton and/or Urquhart.

Schumm discloses the allelic ladders to aid identification of alleles present, and does not teach or suggest any of the STR combinations used in the claimed methods. Schumm does not cure the deficiencies of the other cited references and provides no further insight as to whether the claimed loci could be amplified in a multiplex. Applicants respectfully submit that claims 25-27 are patentable over Schumm, in view of Fregeau, Kimpton and/or Urquhart.

Therefore, in light of the arguments set forth above, Applicants respectfully submit that claims 25-27 of the present application are in condition for allowance, and a favorable action thereon is respectfully requested. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

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